Treatment Rationale and Study Design for Clinical Trial on the Efficacy of UFT/LV for Stage II Colorectal Cancer With Risk Factors for Recurrence (JFMC46-1201)

Sotaro Sadahiro,[1] Satoshi Morita,[2] Kazuaki Sasaki,[3] Kazuhiro Sakamoto,[4] Hiroki Ohge,[5] Takao Takahashi,[6] Takashi Tsuchiya,[7] Toshihiko Sato,[8] Ken Kondo,[9] Yutaka Ogata,[10] Hiroyuki Masuko,[11] Hideo Baba,[12] Kiyoshi Maeda,[13] Madoka Hamada,[14] Michio Itabashi,[15] Genichi Nishimura,[16] Keiichi Takahashi,[17] Masataka Ikeda,[18] Masataka Taguri,[19] Susumu Kodaira[20]

Abstract

Background: The usefulness of adjuvant chemotherapy for stage II colon cancer has not been established. Meanwhile, the presence of stage II colon cancer with high-risk factors for recurrence has been reported. To our knowledge, no prospective study of adjuvant chemotherapy for stage II colon cancer with high-risk factors has been implemented to date. **Patients and Methods:** This study is a prospective nonrandomized controlled study based on patients' selection of treatment option, including randomized therapeutic decision-making, to evaluate the usefulness of adjuvant chemotherapy with tegafur-uracil (UFT) with leucovorin (LV) for stage II colon cancer with high-risk factors for recurrence, compared with surgery alone. Five courses of UFT/LV therapy will be given as follows: UFT (300 mg/m^2/d) with LV (75 mg/d) will be orally administered in 3 doses per day. Treatment will be received daily for 28 days, followed by a 7-day rest or will be received daily for 5 days, followed by a 2-day rest. For both regimens, 1 course will last 5 weeks, and 5 courses will be given. The primary end point is disease-free survival. A propensity score matching will be conducted based on 7 variables that represent risk factors to minimize selection bias in a comparison between the nonrandomized arms. For this nonrandomized comparison, a target sample size is set at 1200 (400 and 800 patients for the surgery alone and UFT/LV groups, respectively) and 1720 patients will be enrolled. In this study we aim to evaluate the therapeutic usefulness of adjuvant chemotherapy with UFT/LV for stage II colorectal cancer with risk factors for recurrence.

Clinical Colorectal Cancer, Vol. 14, No. 4, 277-80 © 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Adjuvant chemotherapy, High-risk stage II, Propensity score matching, Treatment duration, UFT/Leucovorin

This study is registered with University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), protocol ID: UMIN000007783.

[1]Department of Surgery, Tokai University, Isehara, Japan
[2]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan
[3]Department of Surgery, Otaru Ekisaikai Hospital, Otaru, Japan
[4]Department of Coloproctological Surgery, Juntendo University Faculty of Medicine, Tokyo, Japan
[5]Department of Infectious Diseases, Hiroshima University Hospital, Hiroshima, Japan
[6]Department of Surgical Oncology, Gifu University School of Medicine, Gifu, Japan
[7]Department of Surgery, Sendai City Medical Center, Sendai, Japan
[8]Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan
[9]Department of Surgery, Nagoya Medical Center, Nagoya, Japan
[10]Department of Surgery, Kurume University School of Medicine, Fukuoka, Japan
[11]Department of Surgery, Hokkaido Sapporo Kosei Hospital, Sapporo, Japan
[12]Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[13]Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan
[14]Department of Gastrointestinal Surgery Kansai Medical University Hirakata Hospital, Osaka, Japan, Hiroshima, Japan
[15]Department of Surgery 2, Tokyo Women's Medical College, Tokyo, Japan
[16]Department of Surgery, Japanese Red Cross Kanazawa Hospital, Kanazawa, Japan
[17]Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
[18]National Hospital Organization, Osaka National Hospital, Osaka, Japan
[19]Department of Biostatistics, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[20]Nerima General Hospital, Tokyo, Japan

Submitted: Apr 6, 2015; Accepted: May 15, 2015; Epub: May 22, 2015

Address for correspondence: Sotaro Sadahiro, MD, Department of Surgery, Tokai University, 143 Shimokasuya Isehara, Kanagawa 259-1193, Japan
E-mail contact: sadahiro@is.icc.u-tokai.ac.jp

http://dx.doi.org/10.1016/j.clcc.2015.05.004

Introduction

Standard adjuvant chemotherapy for stage III colon cancer consists of 6 months of treatment with fluorouracil (5-FU) with leucovorin (LV), tegafur-uracil (UFT) with LV, capecitabine, and infusional fluorouracil and folinic acid with oxaliplatin (FOLFOX).[1] As for the efficacy of adjuvant chemotherapy for stage II colorectal cancer, positive reports[2] and negative reports[3] have been published, and a definitive consensus has not been reached. Therefore, for stage II colon cancer, the standard treatment is considered to be surgery alone.

Among patients with stage II colorectal cancer, the presence of a subgroup with risk factors for recurrence has been reported. The American Society of Clinical Oncology 2004 guidelines, the European Society for Medical Oncology guidelines, and the National Comprehensive Cancer Network guidelines propose the following risk factors for recurrence: the presence of < 12 dissected lymph nodes, T4 disease, bowel perforation, and poorly differentiated adenocarcinoma and mucinous carcinoma.[4-6] In addition, the presence of circulating tumor cells (CTCs) in peripheral blood ≥ 24 hours after surgery has been reported to be an independent risk factor.[7] Positivity for Carcinoembryonic antigen (CEA) mRNA has been proposed as a surrogate marker for CTCs.[8] However, there has been no prospective study of adjuvant chemotherapy for patients with risk factors for recurrence such as those listed herein.

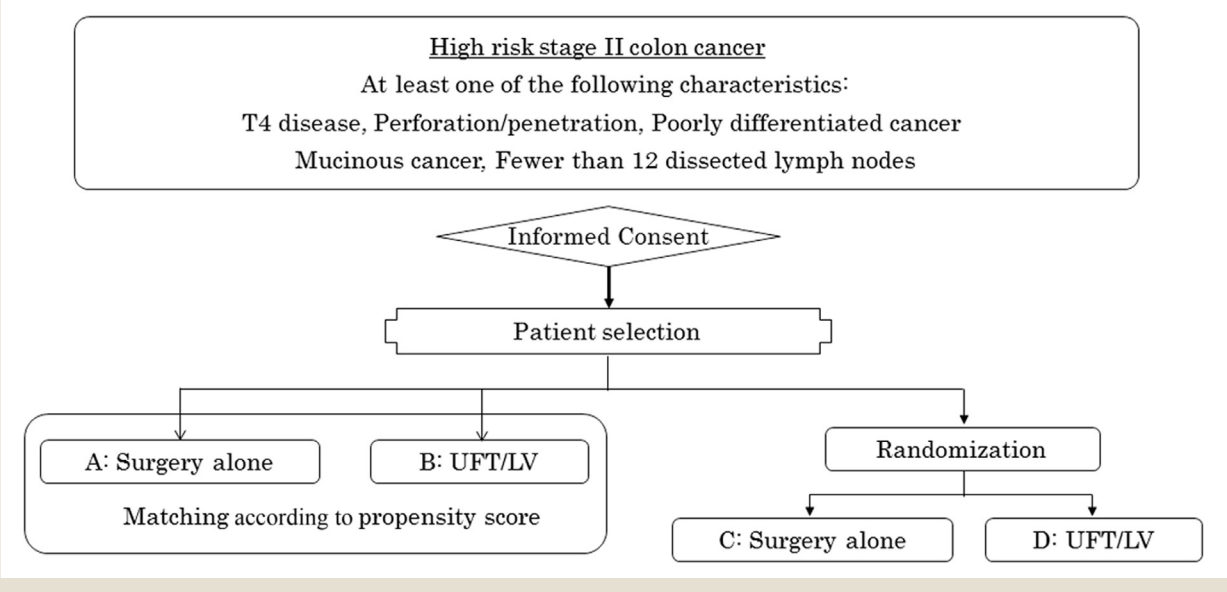
The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study was a randomized clinical trial that compared 5-FU/LV with FOLFOX4 for stage II/III colon cancer.[9] An additive effect of oxaliplatin was obtained with respect to 5-year disease-free survival (DFS) and 6-year overall survival (OS). However, when analyzed according to the disease stage, 5-year DFS and 6-year OS were significantly better in the FOLFOX4 group among patients with stage III colon cancer, but did not differ significantly among patients with stage II colon cancer. UFT/LV for stage II/III colon cancer demonstrated DFS and OS similar to 5-FU/LV in The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-06.[10] UFT/LV has been widely used in Japan. The effectiveness of UFT/LV for stage III colon cancer was demonstrated to be noninferior in 3-year DFS compared with that of 5-FU/LV in Japan Clinical Oncology Group (JCOG) 0205.[11] In the present study, we have planned and started to conduct a clinical trial to compare adjuvant chemotherapy with UFT/LV with surgery alone in patients with stage II colon cancer at high risk for recurrence.

Study Design

The study is a nonrandomized controlled study based on patients' selection of treatment to evaluate the usefulness of adjuvant chemotherapy with UFT/LV for stage II colon cancer with high risk for recurrence compared with surgery alone. Because there is no evidence to indicate that adjuvant chemotherapy is clearly advisable for stage II colon cancer at high risk for recurrence, it was considered difficult to obtain informed consent when the study used a randomized controlled design. Therefore, we conducted a nonrandomized study that would allow patients to choose whether to receive treatment of surgery alone (group A) or with UFT/LV (group B). Patients who are unable to choose treatment are randomly assigned to surgery alone (group C) or UFT/LV (group D; Figure 1).

The primary end point is DFS. Secondary end points are OS, safety, effects on positivity for CEA mRNA ≥ 24 hours after surgery, and outcomes.

Figure 1 Study Schema. Clinical Trial on the Efficacy of UFT/LV for Stage II Colorectal Cancer With Risk Factors for Recurrence: Japanese Foundation for Multidisciplinary Treatment of Cancer 46-1201. CEA mRNA to Be Measured Within 14 Days of Patient Registration in the Trial



Abbreviations: CEA = Carcinoembryonic antigen; UFT/LV = Tegafur-Uracil With Leucovorin.

Participating Institutions

Approximately 300 leading Japanese institutions and hospitals will participate in the study after approval by the internal review board of each institution.

Eligibility Criteria

The inclusion criteria are as follows:

(1) Histologically confirmed stage II colon adenocarcinoma
(2) At least 1 of the following factors:
- T4 disease
- Perforation/penetration
- Poorly differentiated adenocarcinoma
- Mucinous carcinoma
- Fewer than 12 dissected lymph nodes

(3) R0 resection
(4) Age 20 to 80 years
(5) Eastern Cooperative Oncology Group performance status of 0 or 1
(6) No previous treatment other than surgery for the colon cancer
(7) Adequate oral intake
(8) Adequate organ functions as listed:
- Leukocytes: $\geq$ 3000/mm^3 to $<$ 12,000/mm^3
- Neutrophils: $\geq$ 1500/mm^3
- Platelets: $\geq$ 100,000/mm^3
- Hemoglobin: $\geq$ 9.0 g/dL
- Total bilirubin: $\leq$ 2.0 mg/dL
- Aspartate aminotransferase and alanine aminotransferase: $\leq$ 100 IU/L
- Serum creatinine: $<$ 1.5 mg/dL

(9) Treatment can be started within 8 weeks after surgery
(10) Written informed consent.

The exclusion criteria are as follows:

(1) Contraindications for UFT/LV
(2) Multiple active cancers with a disease-free period of $<$ 5 years
(3) Serious postoperative complications
(4) Presence of any of the following comorbidities:
- Uncontrolled diabetes mellitus
- Uncontrolled hypertension
- Hepatic cirrhosis or hepatic failure
- Renal failure
- Interstitial pneumonia, pulmonary fibrosis, or severe emphysema
- Active infection
- Heart failure, myocardial infarction, angina pectoris, or marked electrocardiogram abnormalities within the previous 6 months

(5) Serious diarrhea
(6) History of serious drug hypersensitivity
(7) Concern about pregnancy
(8) Psychosis or psychiatric symptoms
(9) Other reasons as specified by the attending physician.

Treatment Plan

Groups A and C (Surgery Alone)

Patients are followed-up without adjuvant treatment according to a surveillance schedule that includes chest and abdominal computed tomography scans every 6 months, for 5 years until recurrence, other malignancy, or death is confirmed.

Groups B and D (UFT/LV)

Tegafur-uracil/LV will be started within 8 weeks after surgery. Five courses of UFT/LV therapy will be given as follows: UFT (300 mg/m^2/d) with LV (75 mg/d) orally administered in 3 doses per day at approximately 8-hour intervals. Treatment will be received daily for 28 days, followed by a 7-day rest (daily treatment regimen) or will be received daily for 5 days, followed by a 2-day rest (5-day treatment plus 2-day rest regimen; no treatment on Saturdays and Sundays). For both regimens, 1 course will last 5 weeks, and 5 courses will be given.

After the completion of UFT/LV therapy, patients are followed-up according to the same schedule as for groups A and C.

Target Sample Size

The sample size will be determined separately for the nonrandomized arms and the randomized arms, using the same clinical hypotheses. The 3-year DFS is forecast to be 78% in the surgery-alone group and 84% (hazard ratio [HR], 0.7) in the UFT/LV group of this study.

The sample size in the nonrandomized arm (groups A and B), assuming a registration period of 3 years, a follow-up period of 5 years, a 2-sided α level of .05, a power of 80%, and a sample size ratio of 1:2 between the surgery-alone group and the UFT/LV group, is estimated to be 1122 subjects in total. Because some dropouts are expected, the target sample size has been set at 1200 in total (400 in the surgery-alone group and 800 in the UFT/LV group). In other words, the target number of patient pairs to be used for propensity matching has been set at 400. The patient enrollment will be completed when 400 pairs of patients are determined to be analyzed.

Based on prestudy exploratory investigation of historical data at 1 hospital, we expect the matching rate to be 70% at maximum. With this matching rate of 70%, 1715 patients are needed to be enrolled. Considering that this expectation contains substantial uncertainty, we plan to reestimate the number of patients to be accrued by periodically monitoring the matching rate. If the matching rate is more likely to decrease to 60% or 50%, we will increase the number of accrual patients to 2000 or 2400 accordingly.

Statistical Analysis Plan

The final data analysis will be conducted separately for the nonrandomized arms (group A vs. group B) and randomized arms (group C vs. group D). For analysis of the nonrandomized arm, propensity score matching will be used to minimize confounding in comparisons.[12] The potential confounding factors for estimating propensity scores are prespecified as follows: age ($\geq$ 70 or $<$ 70), sex (male or female), number of dissected lymph nodes ($\geq$ 12 or $<$ 12), T4 disease (presence or absence), bowel perforation (presence or absence), poorly differentiated adenocarcinoma (presence or absence), and mucinous carcinoma (presence or absence). The caliper of the propensity score

matching will be determined before the analysis so that the standardized differences of all confounding factors will be < 0.1.[13] Moreover, analysis will be conducted with the inverse probability of treatment-weighting method,[14] based on propensity scores.

The analysis plan for the nonrandomized arms is as follows: a stratified log-rank test will be used to compare arms, taking into account strata for matched pairs in populations to which propensity score matching is applied (2-sided, significance level of 5%). The HR and 2-sided 95% confidence interval (CI) in the UFT/LV group will be calculated using the stratified Cox proportional hazards model. The Kaplan–Meier method will be used to estimate 3-year DFS for each arm and Greenwood formula to calculate the 95% CI. In addition, to examine the influence of interinstitutional variability on the comparison, a sensitivity analysis will be done by excluding hospitals in which > 10 patients are enrolled and more than 80% of them are in either of the surgery-alone and UFT/LV groups. This study is registered with UMIN-CTR, protocol ID: UMIN000007783.

Conclusion

The study is a nonrandomized controlled study based on patients' selection of treatment options to evaluate the usefulness of adjuvant chemotherapy with UFT/LV after curative resection of stage II colon cancer in patients who might be at high risk for recurrence, compared with surgery alone, using propensity score matching in the analysis. Enrollment in this study began in May 2012 and is under way.

Acknowledgments

This study was sponsored by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) with funding from Taiho Pharmaceutical Co Ltd, Japan, under the research contract (JFMC 46-1201). The funding source has no role in the study design, data collection, analysis and interpretation, or decision to submit results for presentation or publication other than providing information on the efficacy and safety of UFT/LV. We thank Mitsuo Kusano, Ichinosuke Hyodo, and Junichi Sakamoto for their work on the Independent Data Monitoring Committee.

Disclosure

Takao Takahashi has received honoraria from Taiho. Hideo Baba has received honoraria from Taiho; and research funding from JFMC and Taiho. Michio Itabashi has received honoraria from Chugai. Keiichi Takahashi has received honoraria from Taiho. Satoshi Morita has received consultancies from Taiho; and honoraria from Taiho. The remaining authors have stated that they have no conflicts of interest.

References

1. Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2012; 17:1-29.
2. Sakamoto J, Ohashi Y, Hamada C, et al. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. *J Clin Oncol* 2004; 22:484-92.
3. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. *J Clin Oncol* 1999; 17:1356-63.
4. National Comprehensive Cancer Network The NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. version 2. 2011. http://www.nccn.org/professionals/physician_gls/recently_updated.asp. Accessed November 29, 2010.
5. Benson AB III, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol* 2004; 22:3408-19.
6. Van Cutsem EJ, Oliveira J. Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* 2008; 19(suppl 2):ii29-30.
7. Peach G, Kim C, Zacharakis E, et al. Prognostic significance of circulating tumour cells following surgical resection of colorectal cancers: a systematic review. *Br J Cancer* 2010; 102:1327-34.
8. Sadahiro S, Suzuki T, Maeda Y, et al. Detection of carcinoembryonic antigen messenger RNA-expressing cells in peripheral blood 7 days after curative surgery is a novel prognostic factor in colorectal cancer. *Ann Surg Oncol* 2007; 14:1092-8.
9. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; 350:2343-51.
10. Lembersky BC, Wieand HS, Petrelli NJ, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol* 2006; 24:2059-64.
11. Shimada Y, Hamaguchi T, Mizusawa J, et al. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. *Eur J Cancer* 2014; 50:2231-40.
12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70:41-55.
13. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28:3083-107.
14. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11:550-60.